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BREATH: Web-Based Self-Management for Psychological Adjustment After Primary Breast Cancer—Results of a Multicenter Randomized Controlled Trial

Sanne W. van den Berg, Marieke F.M. Gielissen, José A.E. Custers, Winette T.A. van der Graaf, Petronella B. Ottevanger, and Judith B. Prins

All authors: Radboud university medical center, Nijmegen, the Netherlands.

Published online ahead of print at www.jco.org on July 13, 2015.

Supported by Pink Ribbon, the Netherlands (Grant No. 2009-2013).

Presented at the International Psycho-Oncology Society 15th World Congress of Psycho-Oncology, Rotterdam, the Netherlands, November 6-8, 2013; and at the 13th International Congress of Behavioral Medicine, Groningen, the Netherlands, August 20-23, 2014.

The study sponsor had no role in the study design, data collection, analysis and interpretation of data, writing of the report, or decision to submit the paper for publication. The authors had full access to all data and had final responsibility for the decision to submit for publication.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Sanne W. van den Berg, MSc, Radboud university medical center, Department of Medical Psychology (840), PO Box 9101, 6500 HB Nijmegen, the Netherlands; e-mail: sanne.vandenberg@radboudumc.nl.

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0732-183X/15/3325w-2763w/\$20.00

DOI: 10.1200/JCO.2013.54.9386

ABSTRACT

Purpose

Early breast cancer survivors (BCSs) report high unmet care needs, and easily accessible care is not routinely available for this growing population. The Breast Cancer E-Health (BREATH) trial is a Web-based self-management intervention to support the psychological adjustment of women after primary treatment, by reducing distress and improving empowerment.

Patients and Methods

This multicenter, randomized, controlled, parallel-group trial evaluated whether care as usual (CAU) plus BREATH is superior to CAU alone. BREATH is delivered in sixteen fully automated weekly modules covering early survivorship issues. Two to 4 months post-treatment, BCSs were randomly assigned to receive CAU + BREATH ($n = 70$) or CAU alone ($n = 80$) using a stratified block design (ratio 1:1). Primary outcomes were distress (Symptom Checklist-90) and empowerment (Cancer Empowerment Questionnaire), assessed before random assignment (baseline, T0) and after 4 (T1), 6 (T2), and 10 months (T3) of follow-up. Statistical (analysis of covariance) and clinical effects (reliable change index) were tested in an intention-to-treat analysis (T0 to T1). Follow-up effects (T0 to T3) were assessed in assessment completers.

Results

CAU + BREATH participants reported significantly less distress than CAU-alone participants (-7.79 ; 95% CI, -14.31 to -1.27 ; $P = .02$) with a small-to-medium effect size ($d = 0.33$), but empowerment was not affected (-1.71 ; 95% CI, 5.20 to -1.79 ; $P = .34$). More CAU + BREATH participants (39 of 70 [56%]; 95% CI, 44.1 to 66.8) than CAU-alone participants (32 of 80 [40%]; 95% CI, 30.0 to 51.0) showed clinically significant improvement ($P = .03$). This clinical effect was most prominent in low-distress BCSs. Secondary outcomes confirmed primary outcomes. There were no between-group differences in primary outcomes during follow-up.

Conclusion

Access to BREATH reduced distress among BCSs, but this effect was not sustained during follow-up.

J Clin Oncol 33:2763-2771. © 2015 by American Society of Clinical Oncology

INTRODUCTION

Women diagnosed with breast cancer face challenges that do not end with treatment completion. The first year after primary treatment, the so-called re-entry phase,¹ is characterized by physical, emotional, and social recovery.² Women report high unmet care needs³ and have to cope with lingering physical and emotional symptoms of treatment, fear of recurrence, decreasing social support, losing the safety net of care providers, and resuming professional and recreational activities.^{2,4-6} Approximately 70% of breast cancer survivors (BCSs; ie, women who have completed primary breast cancer treat-

ment with no evidence of recurrence⁷) adjust well during the re-entry phase, but a substantial proportion report high levels of distress.^{8,9}

Better diagnosis and therapy mean that more women survive breast cancer, and self-management strategies¹⁰ and e-health¹¹ have been proposed as ways to support this growing population. Because approximately half of all BCSs already search the Internet for breast cancer-specific information,¹²⁻¹⁵ the Internet is promising for providing psycho-oncological interventions.¹⁶ However, there are few randomized controlled trials (RCTs) of Web-based interventions to support re-entry adjustment. To date, most Web-based interventions including

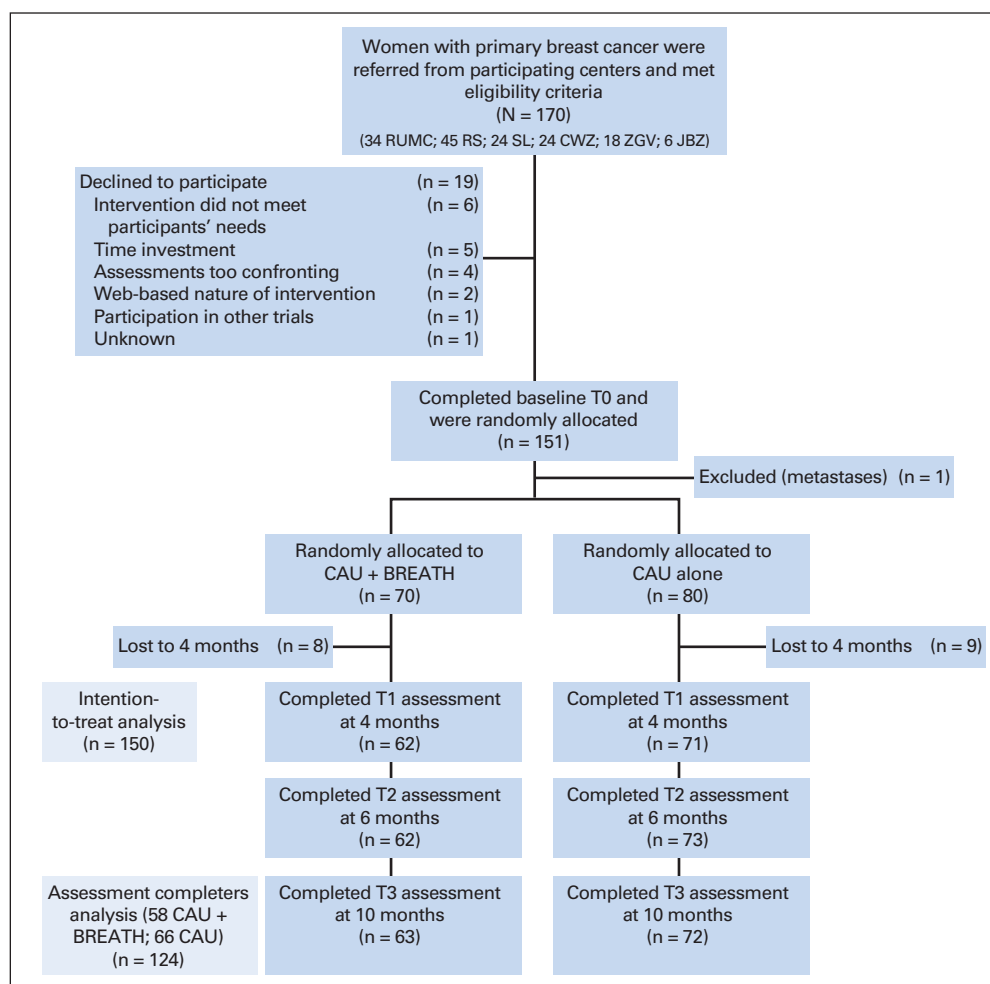


Fig 1. Trial profile. BREATH, Breast Cancer E-Health intervention; CAU, care as usual; CWZ, Canisius-Wilhelmina Hospital, Nijmegen; JBZ, Jeroen Bosch Hospital, Den Bosch; RS, Rijnstate Hospital, Arnhem and Zevenaar; RUMC, Radboud university medical center, Nijmegen; SL, Slingeland Hospital, Doetinchem; ZGV, Hospital Gelderse Vallei, Ede.

women with breast cancer have not been either re-entry specific¹⁷⁻²⁰ or breast cancer specific,^{21,22} or have predominantly focused on peer support groups²³⁻²⁶ or informational support.²⁷ In a recent overview advocating re-entry specific care, Stanton² reported promising but inconclusive evidence from seven RCTs that psychoeducational interventions can be effective in BCSs.

We developed the Breast Cancer E-Health (BREATH) trial,²⁸ a Web-based self-management intervention on the basis of cognitive behavioral therapy that provides early BCSs with self-management skills to enable them to take control of, and adjust to, post-treatment survivorship. The intervention was developed using the transactional model of stress²⁹ and the model of psychological well-being in cancer survivors,³⁰ both of which describe negative and positive outcomes in adapting to a stressor. Thus, the primary aim of this RCT was to study whether care as usual (CAU) plus BREATH (CAU + BREATH) can effectively target negative and positive adjustment. We hypothesized that CAU + BREATH is superior to CAU alone in reducing distress and improving empowerment. Because BCSs exhibit different levels of distress during the re-entry phase, subhypotheses were that CAU + BREATH would reduce distress in high-distress BCSs, keep levels of distress low in low-distress BCSs, and improve empowerment in both distress groups.

PATIENTS AND METHODS

Study Design and Participants

The BREATH study protocol has been published elsewhere.²⁸ We conducted a multicenter, randomized, controlled, parallel-group trial to evaluate the efficacy of a Web-based self-management intervention in facilitating psychological adjustment among BCSs. One university hospital and five regional hospitals in the Netherlands participated (Fig 1). Female BCSs were eligible if they had a histologically proven malignancy of the breast and had completed curative-intent primary treatment (defined as surgery plus adjuvant chemotherapy and/or radiotherapy) 2 to 4 months before the baseline assessment. Participant characteristics are listed in Table 1.

The local treatment team monitored patient recruitment and eligibility and obtained informed consent. A researcher (S.v.d.B.) contacted participants to check additional eligibility criteria: understanding the Dutch language, access to the Internet, and having an e-mail address.

Study assessments covered the first year after breast cancer, with baseline at 2 to 4 months after completion of primary treatment (T0), and follow-up assessments at 4 (T1), 6 (T2), and 10 (T3) months after

Table 1. Baseline Characteristics of Study Participants (N = 150)

Characteristic	CAU + BREATH (n = 70)		CAU alone (n = 80)	
	No. of Patients	%	No. of Patients	%
Age, years				
Mean	51.44		50.18	
SD	8.30		9.15	
Educational level*				
Low (ISCED 0-1-2)	14	20	13	16
Medium (ISCED 3-4-5)	32	46	48	60
High (ISCED 6-7-8)	24	34	19	24
Marital status				
Married/cohabiting	58	83	61	76
Unmarried	5	7	5	6
Divorced	5	7	10	13
Widowed	2	3	4	5
Children (yes)	61	87	62	76
Employment†				
Paid work outside home	30	43	32	40
Home management	21	30	18	23
Unemployed	3	4	8	10
Sick leave	30	43	42	53
Disability insurance act	3	4	5	6
Voluntary work	7	10	4	5
Student	0	0	1	1
Retired	3	4	3	4
Treatment type				
Surgery + chemotherapy + radiotherapy	48	69	56	70
Surgery + chemotherapy	19	27	22	28
Surgery + radiotherapy	3	4	2	2
Hormone therapy	46	66	53	66
Low distress (GSI ≤ 0.57)	51	73	55	69
Frequency of Internet use‡				
Daily	24	59	38	73
2 to 4 times a week	12	29	9	17
Weekly or less	5	12	5	10

NOTE. No significant differences were found between the two conditions ($P > .05$). P values were calculated using χ^2 tests for categorical variables and a two-tailed Student's t test (independent samples) for continuous variables. Abbreviations: BREATH, Breast Cancer E-Health intervention; CAU, care as usual; GSI, General Severity Index; ISCED, International Standard Classification of Education; SD, standard deviation.

*ISCED 2011.

†Percentages do not add up to 100% because more options are possible.

‡CAU + BREATH (n = 41), CAU alone (n = 52).

baseline. The Radboud University Medical Center Medical Review Ethics Committee (file No. 2009/144) and the ethics boards of local participating centers approved the study (Netherlands Trial Register NTR2935).

Intervention

BREATH (Appendix Fig A1, online only) targets re-entry issues relevant to BCSs during a fixed 16-week modular program for four phases of adjustment to breast cancer (looking back, emotional processing, strengthening, and looking ahead).²⁸ Intervention components (104 total) are based on cognitive behavioral therapy and include information (26 scripts), assignment (48 tasks, or homework), assessment (10 self-tests followed by automated feedback), and video (20 topics illustrated with clips extracted

from interviews). BREATH is a pure self-help program without therapist contact (also known as self-administered therapy³¹). Each week, new materials are released, accompanied by standard e-mail reminders, in an attempt to maintain or improve adherence. Access to BREATH was withdrawn after 16 weeks.

BCSs receiving CAU alone did not have access to BREATH. For both conditions, CAU consisted of visits to an oncologist three times per month and psychosocial care on demand or referral. No restrictions were made regarding use of Internet or psychological or other self-help interventions.

Outcomes

Study assessments and random assignment were conducted online using RadQuest software (Radboudumc Medical Psychology, Nijmegen, the Netherlands). Baseline characteristics were obtained with a medical checklist derived from the patient chart.

General psychological distress was assessed with the Symptom Checklist-90 (SCL-90; range, 90-450), which has good psychometric properties in healthy and patient populations.³² The SCL-90 total score showed good internal consistency at baseline (Cronbach's $\alpha = .97$). For the General Severity Index (GSI), which represents the mean score of all responses, transformed item scores (0-4) were used. General psychological empowerment was assessed with the Cancer Empowerment Questionnaire (CEQ).³³ The CEQ presumes that patients can derive strength from themselves (intrapersonal) and from their social surroundings (interpersonal). Baseline internal consistency was good (Cronbach's $\alpha = .92$).

Secondary outcomes reflected negative adjustment (general^{34,35} and cancer-specific distress,³⁶ fatigue,³⁷ helplessness,³⁸ and fear of cancer recurrence^{39,40}) and positive adjustment (self-efficacy,⁴¹ remoralization,⁴² personal control,⁴³ quality of life,⁴⁴ fulfillment,⁴⁵ re-evaluation,⁴⁵ new ways of living,⁴⁵ and valuing life⁴⁵). For details of secondary outcomes, see our study protocol²⁸ (or the legend of Table 2 with treatment effects).

Information about self-reported use of Internet and other resources (individual support, peer support, rehabilitation support groups) was collected at T1. General Internet use was assessed with the question "Have you consulted the Internet for information on (learning to live with) breast cancer in the past 4 months?" Four-month usage data of CAU + BREATH participants were evaluated.⁴⁶ For the current report, correlations were calculated between the mean difference (T0 to T1) in distress and the continuous usage variables of frequency of log-ins, total duration (in minutes), and activity (number of intervention components opened).

Random Assignment and Masking

BCSs were randomly assigned (allocation ratio 1:1) to receive CAU + BREATH or CAU alone. For each center, a randomized block design with stratification by hormone therapy was generated. After baseline assessment, a random number generator with variable block sizes of 4, 6, and 8 automatically ensured blinded allocation until intervention assignment. One researcher (S.v.d.B.) informed participants about treatment assignment by e-mail and was therefore not blinded. In one case, a participant was told an incorrect treatment assignment (CAU instead of CAU + BREATH); this participant received CAU alone and her data were analyzed accordingly.

Statistical Methods

All statistical analyses were performed with SPSS 20 (IBM, Armonk, NY). The sample size calculation for the primary outcomes at T1 was 170: 128 BCSs (64 in each group) at 80% power for differences between CAU + BREATH and CAU alone with a medium effect size of 0.50, plus a 25% dropout rate.²⁸ The level of significance in the sample size calculation was adjusted to $P \leq .025$ to keep the overall chance of type I error at 5%. Inclusion was prematurely stopped at 151 participants, with approval of the ethics committee, because only 5% (7 of 151) of the participants dropped out at T1.

Statistical Effect

The primary hypothesis was that CAU + BREATH would be superior to CAU alone in decreasing distress and increasing empowerment, and it was tested in an intention-to-treat (ITT) analysis of data for T0 and T1. Missing data at T1 were imputed using last observation carried forward. The significance of intervention effects on primary and secondary outcomes was tested using one-way between-groups analyses of covariance with group (CAU + BREATH or CAU alone) as a fixed factor. Because participants were not preselected before inclusion, the analysis of covariance model corrected for baseline differences. For primary outcome analyses, baseline distress (SCL-90) and empowerment (CEQ) were used as covariates. For secondary outcome analyses, baseline scores of corresponding questionnaires were used as covariates. Interaction effects of mean adjusted differences between T0 and T1 by group are reported in Table 2, with SEs, significance level, and 95% CI. Effect size Cohen's d for independent groups was calculated using the pooled standard deviations and unadjusted means on T1.

Clinically Significant Change

Clinically significant change, assessed with the reliable change index (RCI) of the GSI, was tested in ITT analysis (T0 to T1). Following Jacobson and Truax,⁴⁷ Schauenburg and Strack⁴⁸ calculated the GSI cutoff 0.567 to discriminate between low and high distress on the basis of normative and psychotherapy samples. The magnitude of improvement (defined as $RCI \leq -0.16$ for low-distress participants and $RCI \leq -0.43$ for high-distress participants) or deterioration ($RCI \geq 0.16$ for low-distress participants and $RCI \geq 0.43$ for high-distress participants) was assessed using one-sided χ^2 tests.³³

Follow-Up Effect

Follow-up effects for primary and secondary outcomes were evaluated with mixed within-between repeated-measures analysis of variance, including data for participants who completed all four assessments (T0 to T3). Because participants were randomly assigned at each center, center was not included as a random effect. Baseline variables were taken into account as within factors in the model. Differences between CAU + BREATH and CAU alone were tested using independent samples t tests.

RESULTS

Between August 2010 and March 2012, 170 women were referred and 151 (89%) underwent random assignment (Fig 1). Data collection was finalized in February 2013. One woman was errone-

ously enrolled (metastatic disease) and excluded after the random assignment,⁴⁹ leaving a final ITT sample of 150 BCSs (70 CAU + BREATH, 80 CAU alone). At baseline, the two groups did not differ on demographic characteristics (Table 1) and study outcomes (Table 2). Participants with missing data at T1 ($n = 17$) had higher levels of baseline distress than participants with complete data at T1 (mean difference, 23.57; 95% CI, 3.82 to 43.31; $P = .02$). Levels of baseline empowerment were similar ($P = .79$). Missing data at T1 were equally distributed between the two groups. Overall, 124 participants (58 CAU + BREATH; 66 CAU alone) completed all four assessments, and their data were included in follow-up analyses. No metastases or severe illnesses were reported during the study. One woman was admitted to a psychiatric clinic; this was reported as a serious adverse event.

Statistical Effect

The decrease in distress at T1 was significantly greater in CAU + BREATH participants than in CAU-alone participants, with a small-to-medium effect size ($d = 0.33$; Table 2). Baseline distress explained 53% of the variance in distress at T1 ($P < .005$). No such difference in empowerment was found.

Secondary outcome analyses (Table 2) revealed that CAU + BREATH led to significant improvements in five of seven negative adjustment variables (general and cancer-specific distress, fatigue, and two fear of cancer recurrence outcomes) with small-to-medium effect sizes ($d = 0.37$ to 0.55), and in 3 of 10 positive adjustment variables (self-efficacy, remoralization, new ways of living) with small-to-medium effect sizes ($d = 0.26$ to 0.39).

Clinically Significant Change

More CAU + BREATH participants (39 of 70 [56%]; 95% CI, 44.1 to 66.8) than CAU-alone participants (32 of 80 [40%]; 95% CI, 30.0 to 51.0) showed a clinically significant improvement ($P = .03$). We had hypothesized that more high-distress BCSs would show a clinically significant improvement after CAU + BREATH than after CAU alone, but this was not the case (10 of 21 [48%]; 95% CI, 28.3 to 67.6 v 14 of 27 [52%]; 95% CI, 34.0 to 69.3, respectively; $P = .39$). Post hoc analysis revealed that there was no difference in the proportion of high-distress BCSs showing clinical deterioration (5 of 21 [24%] v 2 of 27 [7%], respectively; $P = .06$). Of the low-distress BCSs, more CAU + BREATH participants than CAU-alone participants showed clinical improvement or no change (41 of 49 [84%]; 95% CI, 71.0 to 91.5 v 35 of 53 [66%]; 95% CI, 52.6 to 77.3 respectively; $P = .02$). Moreover, explorative post hoc analyses of low-distress BCSs revealed that, compared with CAU-alone participants, CAU + BREATH participants showed more clinically significant improvement (29 of 49 [59%] v 18 of 53 [34%], respectively; $P = .006$) and less deterioration (8 of 49 [16%] v 18 of 53 [34%], respectively; $P = .02$). The empowerment hypothesis was not tested, because empowerment was not significantly different between CAU + BREATH and CAU alone.

Follow-Up Effect

At T2 and T3, distress was significantly reduced regardless of group assignment ($F[3, 120] = 5.88$; $P = .001$; Fig 2). This was also true for the secondary negative adjustment outcomes of fear of cancer recurrence (Cancer Worry Scale; $F[3, 120] = 5.954$; $P = .001$), fatigue ($F[3, 120] = 4.40$; $P = .006$), and helplessness ($F[3, 120] = 11.964$; $P = .000$). A significant time \times group interaction effect was found for

Table 2. Effect of Treatment (intention-to-treat analysis) on Primary and Secondary Outcomes After 4 Months (N = 150)

Treatment Effect	Mean (SD/SE)		Mean Difference (95% CI)	P	Effect Size (Cohen's <i>d</i>)
	CAU + BREATH (n = 70)	CAU Alone (n = 80)			
Primary outcomes					
Distress (SCL-90* ³²)					
T0	135.44 (37.532)	140.33 (41.045)	−4.882 (−17.640 to 7.875)	.451	
T1 (unadjusted)	124.90 (26.956)	135.84 (37.975)			
T1 (adjusted)	126.676 (2.412)	134.463 (2.250)	−7.788 (−14.308 to −1.267)	< .05	0.33
Empowerment (CEQ† ³³)					
T0	156.90 (13.222)	154.06 (15.133)	2.838 (−1.779 to 7.454)	.226	
T1 (unadjusted)	159.13 (15.116)	155.45 (13.639)			
T1 (adjusted)	157.946 (1.293)	156.240 (1.206)	1.706 (−1.787 to 5.200)	.336	0.16
Secondary outcomes					
Negative adjustment variables					
General (distress [HADS-total score]* ³⁵)					
T0	9.07 (6.710)	10.01 (7.259)	−0.941 (−3.208 to 1.326)	.413	
T1 (unadjusted)	7.67 (6.033)	9.89 (6.129)			
T1 (adjusted)	8.052 (0.461)	9.621 (0.431)	−1.569 (−2.815 to −0.322)	< .05	0.37
General (Distress Thermometer*)					
T0	3.89 (2.505)	4.53 (2.516)	−0.639 (−1.451 to 0.173)	.122	
T1 (unadjusted)	3.46 (2.506)	4.00 (2.408)			
T1 (adjusted)	3.662 (0.249)	3.858 (0.232)	−0.196 (−0.868 to 0.477)	.566	0.22
General (fatigue [CIS]* ³⁷)					
T0	33.29 (12.530)	33.38 (12.627)	−0.089 (−4.159 to 3.980)	.965	
T1 (unadjusted)	28.57 (12.913)	32.77 (13.309)			
T1 (adjusted)	28.602 (1.205)	32.746 (1.127)	−4.144 (−7.404 to −0.884)	< .05	0.32
Cancer specific (fear of recurrence [CWS]* ³⁹)					
T0	14.31 (4.454)	15.36 (3.892)	−1.048 (−2.395 to 0.298)	.126	
T1 (unadjusted)	13.13 (3.310)	15.19 (4.119)			
T1 (adjusted)	13.452 (0.296)	14.799 (0.277)	−1.347 (−2.149 to −0.545)	< .001	0.55
Cancer specific (fear of recurrence [CAS]* ⁴⁰)					
T0	5.11 (1.584)	5.45 (1.630)	−0.336 (−0.856 to 0.856)	.204	
T1 (unadjusted)	4.90 (1.395)	5.51 (1.567)			
T1 (adjusted)	5.015 (0.120)	5.398 (0.112)	−0.383 (−0.707 to −0.059)	< .05	0.41
Cancer specific (helplessness [ICQ]* ³⁸)					
T0	10.36 (3.301)	10.21 (3.133)	0.145 (−0.894 to 1.184)	.784	
T1 (unadjusted)	9.39 (2.975)	9.45 (3.023)			
T1 (adjusted)	9.335 (0.274)	9.488 (0.256)	−0.153 (−0.894 to 0.589)	.685	0.02
Cancer specific [distress (IES-total score)* ³⁶)					
T0	18.11 (15.098)	18.88 (15.730)	−0.761 (−5.754 to −4.232)	.764	
T1 (unadjusted)	11.81 (12.240)	17.35 (14.371)			
T1 (adjusted)	12.024 (1.244)	17.143 (1.164)	−5.119 (−8.486 to −1.752)	< .01	0.42
Positive adjustment variables					
General (self-efficacy [SES]† ⁴¹)					
T0	19.97 (2.756)	20.30 (2.655)	−0.329 (−1.203 to 0.545)	.459	
T1 (unadjusted)	21.03 (3.217)	20.23 (2.556)			
T1 (adjusted)	21.130 (0.290)	20.133 (0.271)	0.997 (0.213 to 1.781)	< .05	0.28
General (remoralization [RS12]† ⁴²)					
T0	3.09 (0.512)	3.06 (0.569)	0.022 (−0.153 to 0.198)	.802	
T1 (unadjusted)	3.28 (0.495)	3.08 (0.540)			
T1 (adjusted)	3.275 (0.051)	3.081 (0.047)	0.195 (0.058 to 0.332)	< .01	0.39
General (personal control [Mastery]†)					
T0	23.93 (4.604)	23.64 (4.653)	0.291 (−1.206 to 1.789)	.701	
T1 (unadjusted)	24.74 (4.548)	23.58 (4.957)			
T1 (adjusted)	24.655 (0.435)	23.677 (0.407)	0.977 (−0.199 to 2.154)	.103	0.24
General (acceptance [ICQ]†)					
T0	16.17 (3.996)	16.14 (3.525)	0.034 (−1.180 to 1.247)	.956	
T1 (unadjusted)	17.60 (4.109)	16.94 (3.509)			
T1 (adjusted)	17.586 (0.313)	16.948 (0.293)	0.637 (−0.209 to 1.1484)	.139	0.17
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Table 2. Effect of Treatment (intention-to-treat analysis) on Primary and Secondary Outcomes After 4 Months (N = 150) (continued)

Treatment Effect	Mean (SD/SE)		Mean Difference (95% CI)	P	Effect Size (Cohen's <i>d</i>)
	CAU + BREATH (n = 70)	CAU Alone (n = 80)			
General (perceived benefits [ICQ]†)					
T0	15.09 (4.169)	15.86 (3.801)	−0.777 (−2.063 to 0.509)	.235	
T1 (unadjusted)	15.66 (4.584)	16.21 (4.541)			
T1 (adjusted)	16.042 (0.363)	15.926 (0.339)	0.116 (−0.866 to 1.098)	.816	0.12
Cancer specific (quality of life [EORTC QLQ-C30]† ⁴⁰)					
T0	66.79 (16.575)	69.79 (17.906)	−3.006 (−8.601 to 2.589)	.290	
T1 (unadjusted)	72.50 (18.572)	70.52 (15.231)			
T1 (adjusted)	73.295 (1.784)	69.882 (1.666)	3.413 (−1.411 to 8.236)	.164	0.12
Cancer specific (fulfillment [PAQ]† ⁴⁵)					
T0	38.30 (6.686)	39.80 (6.934)	−1.500 (−3.706 to 0.706)	.181	
T1 (unadjusted)	40.89 (6.728)	40.10 (7.289)			
T1 (adjusted)	41.284 (0.759)	39.788 (0.708)	1.496 (−0.55 to 3.548)	.152	0.11
Cancer specific (re-evaluation [PAQ]†)					
T0	38.39 (6.160)	40.01 (6.407)	−1.627 (−3.662 to 0.409)	.116	
T1 (unadjusted)	38.81 (6.493)	39.44 (7.107)			
T1 (adjusted)	39.380 (0.611)	38.835 (0.570)	0.545 (−1.107 to 2.197)	.516	0.09
Cancer specific (new ways of living [PAQ]†)					
T0	41.19 (5.279)	41.34 (7.488)	−0.152 (−2.271 to 1.967)	.888	
T1 (unadjusted)	42.94 (6.230)	41.07 (8.012)			
T1 (adjusted)	43.001 (0.709)	41.032 (0.663)	1.969 (0.051 to 3.886)	< .05	0.26
Cancer specific (valuing life [PAQ]†)					
T0	34.06 (5.778)	34.51 (4.963)	−0.455 (−2.188 to 1.278)	.604	
T1 (unadjusted)	34.40 (6.087)	34.11 (5.972)			
T1 (adjusted)	34.595 (0.545)	33.971 (0.510)	0.623 (−0.853 to 2.100)	.405	0.05

NOTE. All *P* values were calculated using an analysis of covariance with adjustment for baseline value. (Unadjusted) means unadjusted for baseline covariates. (Adjusted) means adjusted for baseline value of the corresponding questionnaire. Bold font indicates significant effect and corresponding effect size.

Abbreviations: BREATH, Breast Cancer E-Health intervention; CAS, Cancer Acceptance Scale; CAU, care as usual; CEQ, Cancer Empowerment Questionnaire; CIS, Checklist Individual Strength; CWS, Cancer Worry Scale; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items; HADS, Hospital Anxiety and Depression Scale; ICQ, Illness Cognition Questionnaire; IES, Impact of Event Scale; PAQ, Positive Adjustment Questionnaire; RS12, Remoralization Scale-12 items; SCL-90, Symptom Checklist-90 items; SD, standard deviation; SES, Self-Efficacy Scale.

*Increase represents worsening; decrease represents improvement.

†Increase represents improvement; decrease represents worsening.

fear of cancer recurrence (Cancer Worry Scale; $F[3, 120] = 4.563$; $P = .005$), with CAU + BREATH participants reporting less fear than CAU-alone participants at T2 (-1.459 ; 95% CI, -2.743 to -0.175). Of the positive adjustment outcomes, acceptance significantly improved in both groups (ICQ; $F[3, 120] = 8.531$; $P = .000$). Time effects and time \times group interactions were not significant for all remaining outcomes, including empowerment (Fig 3).

Use of BREATH and Other Resources

Use of the BREATH intervention varied considerably. Frequency of logins ranged from 0 to 45, total duration ranged from 0 to 2,324 minutes, and activity ranged from 0 to 104 intervention components opened. The mean difference in distress (SCL-90, T0 to T1) was not correlated with frequency ($r = -0.007$; $P = .96$), total duration ($r = 0.000$; $P = 1.00$), or activity ($r = -1.072$; $P = .55$).

At T1, similar proportions of women in CAU + BREATH and CAU alone had consulted the Internet in the previous 4 months on a monthly (24% ν 34%), weekly (13% ν 8%), or daily (0% ν 2%) basis, or not at all (61% ν 58%). There were also no significant differences ($n = 126$; $P = .27$) between CAU + BREATH and CAU-alone participants in the use of individual support (eg, psychologist; 12% ν 25%, respectively), peer and rehabilitation support groups (14% ν 12%, respectively), or combined individual and group support (21% ν 13%,

respectively). Half of the participants in both groups did not make use of other support (53% ν 50%, respectively).

DISCUSSION

At the start of the re-entry phase, 4-month access to BREATH in addition to CAU resulted in a statistically and clinically significant distress reduction compared with CAU alone. However, this small-to-medium effect was not sustained, and levels of distress were similar at 6 and 10 months. CAU + BREATH participants also showed a greater decrease than CAU-alone participants in fear of cancer recurrence, fatigue, and general and cancer-related distress. The effect of BREATH on fear of cancer recurrence was sustained during follow-up. Access to BREATH did not influence empowerment or clinical distress improvement in high-distress BCSs. Low-distress BCSs showed a greater clinical improvement and less deterioration with CAU + BREATH than with CAU alone.

The RCT was designed according to quality standards (CONSORT for parallel group,⁵⁰ nonpharmacologic treatment,⁵¹ and eHealth trials).^{52,53} Statistically and clinically significant changes were evaluated in ITT analyses, with missing data imputed using a conservative method (last observation carried forward)

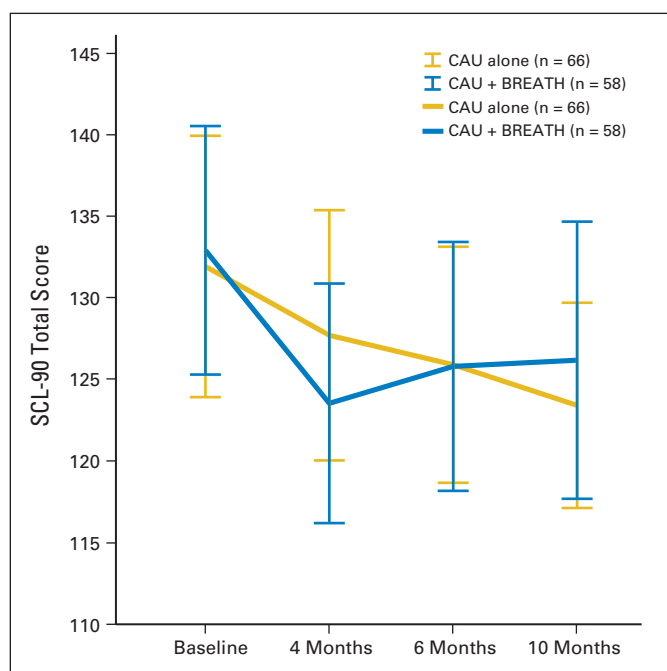


Fig 2. Psychological distress (Symptom Checklist-90 [SCL-90]) at baseline and 4, 6, and 10 months after baseline (n = 124 assessment completers). Vertical bars represent the 95% CI of the mean SCL-90 at each time point. BREATH, Breast Cancer E-Health intervention;; CAU, care as usual.

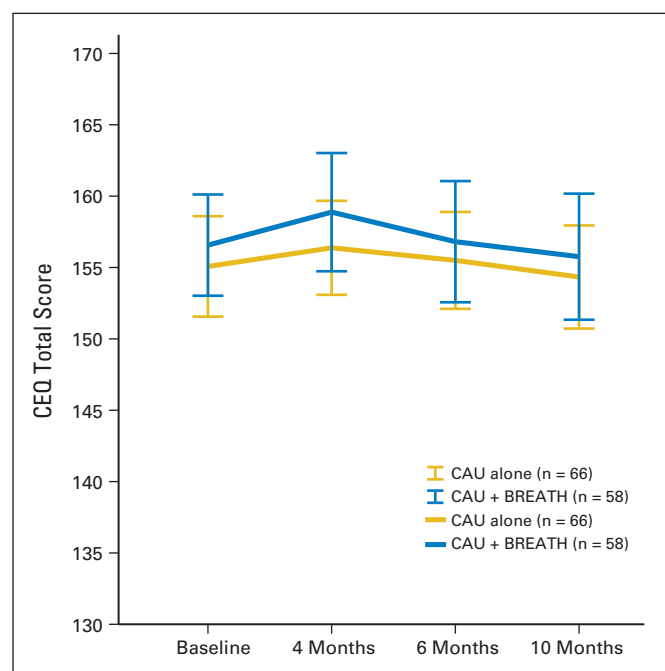


Fig 3. Psychological empowerment (Cancer Empowerment Questionnaire [CEQ]) at baseline and 4, 6, and 10 months after baseline (n = 124 assessment completers). Vertical bars represent the 95% CI of the mean CEQ at each time point. BREATH, Breast Cancer E-Health intervention;; CAU, care as usual.

because the patients in our sample were expected to improve on distress over the study period.^{8,9} The multicenter recruitment strategy guaranteed referrals from both secondary and tertiary care centers. The recruitment procedure, which ensured minimal involvement of the research team, and lack of assistance regarding intervention use and adherence support the ecological validity of BREATH. In the absence of RCTs evaluating similar unguided Web-based interventions for BCSs, the effect size of BREATH is consistent with that of two recent meta-analyses of guided face-to-face (effect size range 0.26 to 0.38)⁵⁴ and Web-based (effect size range, 0.17 to 0.21)⁵⁵ interventions for people with cancer⁵⁴ and chronic somatic conditions.⁵⁵

The secondary outcomes revealed that CAU + BREATH decreased general and cancer-specific distress, fatigue, and fear of cancer recurrence, which may reflect the multicomponent nature of distress in cancer patients.⁵⁶ The clinical relevance of these outcomes needs to be addressed in future research.

CAU + BREATH did not significantly change empowerment relative to the effect of CAU alone and had inconsistent effects on the secondary positive adjustment variables. The study of positive adjustment is a new research area and poses multiple challenges. Although new models of survivorship care stress patient empowerment,^{57,58} there is no consensus about the empowerment construct. Consequently, positive adjustment questionnaires, such as the CEQ, are new, but not extensively validated in BCSs and lack information on sensitivity to change. Furthermore, in psycho-oncology, resource-oriented therapeutic models⁵⁹ are lacking, and interventions are traditionally aimed at diminishing deficits instead of enhancing strengths. It is possible that BREATH does not include a sufficient number of empowerment modules (only 4 of the 16 weekly modules targeted empowerment).

Results should be considered with caution for several reasons. Consistent with the scarce literature on Web-based interventions for cancer patients,⁶⁰ BREATH did not have a sustained effect on distress. This may be because access to the Web site was for 4 months only. Although the limited access enabled accurate postintervention assessments, in retrospect it might have been better to allow participants to retain access, especially because information often remains available with other psychoeducational interventions or self-help books. Another explanation for lack of a sustained effect may be the small-to-medium effect size, which might not have been enough to compensate for the natural course of emotional recovery. The missing-at-random assumption for imputation was violated. BCSs with missing data for the 4-month assessment had significantly higher levels of distress at baseline. Although not significant, more high-distress BCSs in the CAU + BREATH group showed a clinical deterioration. This leads to a cautious interpretation of the results regarding high-distress BCSs, and suggests that these women may need a more intensive intervention than BREATH.

The limited data on BREATH use means it is not possible to draw firm conclusions about how often the intervention should be used to have an effect. Further investigations with larger samples, mediation analyses, or usage pattern are needed to gain insight into determinants of intervention use and to study a possible dose-response relationship.⁶¹ Data for BCSs who declined to participate were not recorded. Although it was not feasible to recruit patients consecutively, our sample seemed homogeneous and representative, because the mean age, treatment type, education, and work situation of participants were comparable to those of other studies evaluating the Dutch breast cancer population.^{3,9,62,63} The study sample also proved representative with regard to psychological

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Sanne W. van den Berg, Petronella B. Ottevanger, Judith B. Prins

Administrative support: Sanne W. van den Berg

Provision of study materials or patients: Petronella B. Ottevanger

Collection and assembly of data: Sanne W. van den Berg

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

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Acknowledgment

We thank all patients who gave their time to participate and the oncologists, radiotherapists, and research nurses of the participating hospitals: Radboud university medical center, Nijmegen; Rijnstate, Arnhem and Zevenaar; Slingeland, Doetinchem; Hospital Gelderse Vallei, Ede; Canisius-Wilhelmina Hospital, Nijmegen; and Jeroen Bosch, Den Bosch.

Appendix

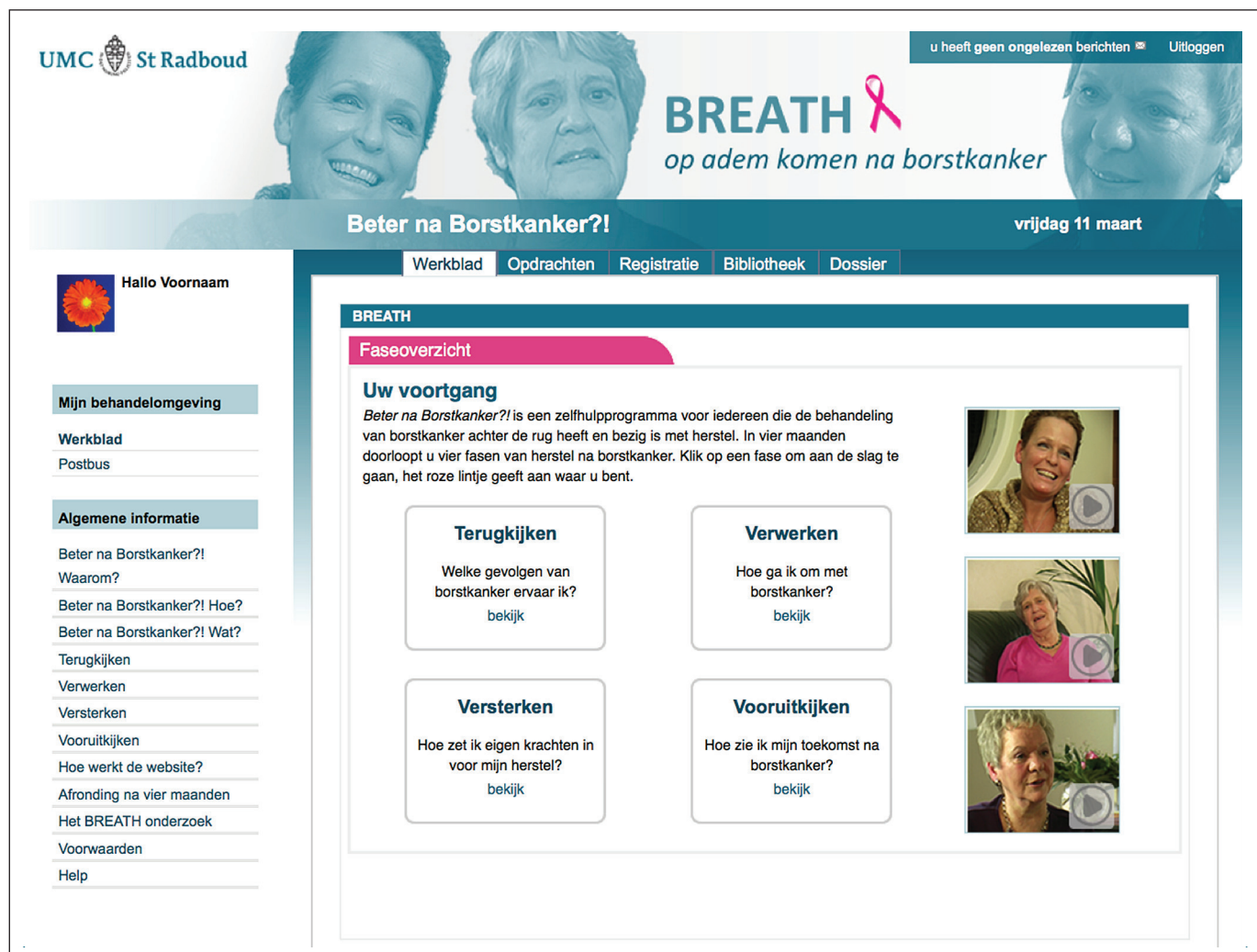


Fig A1. Screenshot of the BREATH (Breast Cancer E-Health intervention) Web site (in Dutch) with four-phase structure.